



α -酮戊二酸在代谢综合征中的研究进展*

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【摘要】 α -酮戊二酸(alpha-ketoglutarate, α -KG)是三羧酸循环的内源性中间代谢产物,参与多种细胞代谢途径,作为能量供体、氨基酸前体、表观遗传调控因子发挥作用。 α -KG还具有免疫调控、缓解氧化应激、延缓衰老等生理功能。近年来,研究发现体内 α -KG水平与代谢综合征,如肥胖和高血糖等病理因素密切相关。外源性补充 α -KG可以改善代谢综合征相关的肥胖程度、血糖水平以及心血管疾病风险等,同时参与调节代谢综合征共同的病理机制,提示 α -KG在代谢综合征中的潜在应用价值。本文以 α -KG和代谢综合征为主题,结合最新研究发现,综述 α -KG在改善代谢综合征的病理发生和疾病发展等方面的研究动态,为进一步探究 α -KG在代谢综合征中的应用提供理论基础。未来研究或围绕代谢综合征的共同致病机理,研究 α -KG能否实现代谢综合征的“异病同治”的治疗目标。

【关键词】 α -酮戊二酸 代谢综合征 肥胖 高血糖 免疫调控 代谢 综述

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【Abstract】 Alpha-ketoglutarate (α -KG), an endogenous intermediate of the tricarboxylic acid cycle, is involved in a variety of cellular metabolic pathways. It serves as an energy donor, a precursor of amino acid biosynthesis, and an epigenetic regulator. α -KG plays physiological functions in immune regulation, oxidative stress, and anti-aging as well. In recent years, it has been reported that the level of α -KG in the body is closely associated with metabolic syndrome, including obesity, hyperglycemia, and other pathological factors. Exogenous supplementation of α -KG improves obesity, blood glucose levels, and cardiovascular disease risks associated with metabolic syndrome. Furthermore, α -KG regulates the common pathological mechanisms of metabolic syndrome, suggesting the potential application prospect of α -KG in metabolic syndrome. In order to provide a theoretical basis for further exploration of the application of α -KG in metabolic syndrome, we focused on α -KG and metabolic syndrome in this article and summarized the latest research progress in the role of α -KG in improving the pathological condition and disease progression of metabolic syndrome. For the next step, researchers may focus on the co-pathogenesis of metabolic syndrome and investigate whether α -KG can be used to achieve the therapeutic goal of "homotherapy for heteropathy" in the treatment of metabolic syndrome.

【Key words】 Alpha-ketoglutarate Metabolic syndrome Obesity Hyperglycemia Immunoregulation Metabolism Review

代谢综合征是一类以肥胖、高血糖、高血压、血脂异常等代谢紊乱作为临床特征,严重危害机体健康的临床症候群^[1]。流行病学调查的结果提示代谢综合征已成为一种全球流行性疾病,全球患病率大约为世界人口的四分之一^[2]。在中国,20岁以上居民的代谢综合征患病率为31.1%,年龄超过75岁的人群中代谢综合征患病率最高(44.2%)^[3]。目前的治疗方式首先建议通过调整饮食和锻炼控制。临床治疗需要运用降压药、降糖药和(或)降脂药的多重组合,针对性地控制相应指标水平^[4-5]。但是,在实际情况中不少患者由于无法坚持节食、运动、多重用

药或者由于药物副作用等原因,导致依从性低,致使全球代谢综合征患病率仍在逐年攀升^[2]。

α -酮戊二酸(alpha-ketoglutarate, α -KG)是三羧酸循环中的中间代谢产物,为细胞活动提供能量ATP,并参与蛋白质、脂肪酸等营养物质的代谢过程^[6]。近年来,研究发现体内 α -KG含量变化与代谢综合征的疾病发生以及相关的肥胖指标和血糖水平等密切相关。补充 α -KG在改善肥胖,调节血脂、血糖、血压等方面具有积极作用,并且阻止病症进一步恶化为心肌梗死等心血管疾病,后者在我国乃至全球居各种原因的首位^[7-8]。从病理机制的角度, α -KG参与调控胰岛素抵抗、氧化应激^[9]、代谢炎症^[10-11],符合通过调节代谢综合征的三大共同病理机制进行“异病同治”的理念^[12]。本文就代谢小分子 α -KG与代谢综合征发生发展相关的研究进行综述,以期对代谢综

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合征的预防和治疗提供一个新的视角。

1 α -KG概述

α -KG在代谢活动中起着重要作用(图1)。首先,三羧酸循环是三大营养物质(糖类、脂肪、氨基酸)代谢的中心枢纽。三羧酸循环在线粒体基质中通过一系列反应将 α -KG在内的中间产物转化为能量载体^[13],为最后的氧化磷酸化反应提供足够的代谢物和底物,以维持细胞内稳态和功能^[14]。外源性 α -KG可以进入三羧酸循环,通过氧化磷酸化途径参与ATP产生,从而为细胞提供能量^[15]。

α -KG也参与到氨基酸代谢中。作为三羧酸循环与谷氨酰胺代谢之间的枢纽^[16], α -KG是谷氨酸、谷氨酰胺和精氨酸的前体物质, α -KG可以通过谷氨酸脱氢酶(GDH)转化为谷氨酸,所得谷氨酸可以通过谷氨酰胺合成酶(GS)进一步代谢为谷氨酰胺,因此 α -KG参与氨基酸和蛋白质的生物合成^[17]。

此外, α -KG是2-氧戊二酸依赖性双加氧酶(2-OGDDs)发挥作用的共底物^[18]。2-OGDDs是一大类保守的负责催化不同底物(如蛋白质、脂类、核酸)羟基化反应的酶。具体而言,2-OGDDs包括DNA去甲基酶和组蛋白去甲基酶,参与表观遗传调控。在胶原蛋白生物合成中,2-OGDDs催化内质网中前胶原蛋白多肽的修饰。2-OGDDs也负责催化肉碱生物合成,介导脂肪酸转运至线粒体并参与脂肪酸稳态^[19]。

2 体内 α -KG水平与代谢综合征的相关性

2.1 α -KG水平与代谢综合征的病因相关

代谢综合征主要是由于高脂、高碳水化合物膳食结构以及久坐不动、运动量少的生活习惯,导致能量摄入高于能量消耗而发生。在能量摄入方面,高脂饮食处理8周和16周的小鼠心脏组织中观察到DNA羟化酶中Tet3的表达上调,并伴随Tet酶的共底物 α -KG的含量显著下降,这可能归因于高脂饮食通过氧化应激导致线粒体缺陷^[20]。另一项研究也发现饮食诱导的肥胖(DIO)小鼠的血浆 α -KG水平明显低于对照组小鼠^[21]。

在能量消耗方面,运动会增加肌肉 α -KG合成和血液 α -KG水平。通过代谢组学比较小鼠抗阻运动(如爬梯子)前后血液以及肌肉组织中 α -KG含量,发现抗阻运动会时间依赖性地增加小鼠血液中 α -KG浓度,其浓度比运动前高1.6倍^[22]。同样地,小鼠进行耐力运动(如跑步)后,血液中 α -KG含量同样显著增加^[22]。研究者进一步发现小鼠运动后的胫骨前肌、腓肠肌等多个部位肌肉组织中 α -KG水平均持续增加^[22]。

2.2 α -KG水平随着代谢综合征发展下降

体内 α -KG含量与肥胖有密切关系。一项比较健康受试者与肥胖患者皮下白色脂肪组织(WAT)的蛋白组学临床研究发现,肥胖患者WAT中谷氨酸丙酮酸转氨酶1和2的表达均下调(分别在细胞质和线粒体中催化谷氨酸转化为 α -KG),这提示 α -KG可能与人类肥胖存在着内在联系^[23]。另有研究在45名受试者的临床化验结果中发现,成年人血浆中 α -KG水平与多种代谢指标均呈现负相关性,其中包括体质量指数(BMI)、臀围、腰围、体脂量和体质量等^[22]。

肥胖者,尤其是中心型肥胖者血液中较高的游离脂肪酸水平往往会引发血糖异常升高。YUAN等^[21]发现db/db糖尿病小鼠血浆 α -KG水平显著低于对照组小鼠的一半水平,进一步在人和小鼠中同时发现血浆 α -KG浓度与血液中糖化血红蛋白(HbA1c)存在负相关关系。与此同时,其他TCA循环相关代谢物与血浆HbA1c水平呈正相关,包括谷氨酰胺、琥珀酸和富马酸等^[21]。

研究表明血浆支链氨基酸(BCAA)升高水平可用于预测2型糖尿病的发展^[24]。BCAA的分解代谢中BCAA的氨基的主要受体是 α -KG(图1),2型糖尿病中 α -KG的不足是导致BCAA积累的主要原因之一^[25-26]。

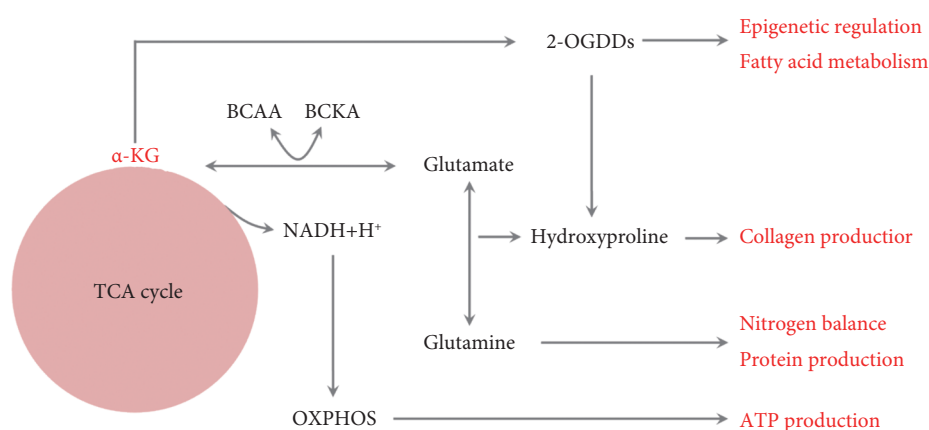
α -KG作为一种存在于人体内的天然小分子,其体内含量常常受到病理情况的干扰,并与代谢综合征病因、肥胖、血糖水平等存在相关性, α -KG可能是预防或治疗代谢综合征的潜在药物成分。

3 α -KG参与调节代谢综合征的潜在机制

虽然关于代谢综合征的发病机制仍未被完全阐明,但是胰岛素抵抗、氧化应激和慢性代谢性炎症被认为是代谢综合征各组分发生及其随后向心血管疾病发展的三大病理生理基础^[27-29]。在代谢综合征发生发展的过程中,这三者之间互为因果,形成恶性循环^[30]。

3.1 α -KG改善胰岛素抵抗

胰岛素抵抗是一系列代谢综合征的病理机制,其本质是胰岛素敏感性的降低和(或)胰岛素反应的下降^[31],其打破血糖、血脂稳态以及血管舒张和血管收缩之间的平衡^[32]。一项临床研究通过代谢组学比较胰岛素抵抗的肥胖女性患者中运动减肥干预前后的血浆代谢模式,筛选出运动干预前与空腹血糖浓度、运动干预后与胰岛素敏感性均显著相关的唯一代谢物为 α -KG^[33]。另外多项研究通过口服葡萄糖耐量测试表明口服 α -KG提高了长期高脂饮食小鼠的胰岛素敏感性,缓解胰岛素抵抗的病理状态^[21, 34-36]。

图1 α -KG的代谢过程Fig 1 The metabolic process of α -KG

TCA: tricarboxylic acid; 2-OGDDs: 2-oxoglutarate dependent dioxygenases; BCAA: branched-chain amino acids; BCKA: branched-chain keto acid; NADH: nicotinamide adenine dinucleotide; OXPHOS: oxidative phosphorylation; ATP: adenosine triphosphate.

3.2 α -KG调节氧化应激

氧化应激是活性氧(ROS)在体内产生的负面结果,可直接对细胞及其内蛋白质或DNA分子造成损害,触发或加重代谢综合征的病理生理过程,诱导血糖、血压、血脂等多方面的代谢紊乱^[37]。

α -KG是一种抗氧化物质,通过酶促和非酶促两种途径发挥抗氧化应激作用,清除生物体内ROS^[38]。 α -KG可以激活抗氧化相关酶的活性,包括超氧化物歧化酶(SOD)、过氧化氢酶(CAT)和谷胱甘肽过氧化物酶(GSH-Px)^[17,39-40]。在非酶促途径中,由于 α -KG的化学结构可以直接破坏活性氧(例如 H_2O_2)的分子结构,从根源上降低其氧化毒性(图2)。 α -KG中 α -碳原子上的酮基与 H_2O_2 反应发生氧化脱羧作用,形成相应的琥珀酸、 CO_2 ^[41]。

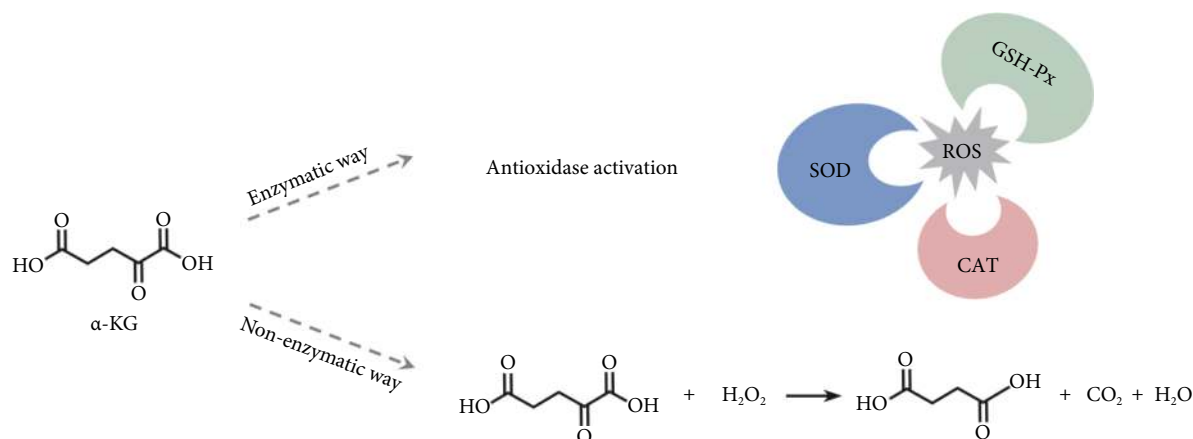
线粒体代谢紊乱是ROS的主要来源。线粒体自噬通

过消除受损的细胞器和不需要的蛋白质来维持线粒体稳态和功能^[42]。FAULKNER等^[43]在2型糖尿病患者肌肉周围细胞的体外模型中发现 α -KG通过线粒体自噬改善氧化还原平衡和线粒体功能。AN等^[44]在心衰小鼠模型中发现 α -KG通过促进线粒体自噬清除受损线粒体并减少ROS产生,改善了小鼠心功能不全。另外在骨关节炎、高脂血症等多种动物疾病模型中发现 α -KG通过诱导线粒体自噬,缓解氧化应激水平^[45-46]。

3.3 α -KG的免疫调控作用

脂肪堆积等因素造成机体全身形成慢性低度炎症微环境,也被称为“代谢炎症”,这是一系列与肥胖相关的代谢综合征的病因学基础^[47]。

巨噬细胞是肥胖患者脂肪组织中最丰富的免疫细胞^[48],同时也是慢性代谢炎症的重要组成部分^[49]。在骨髓来源的巨噬细胞(BMDM)、单核巨噬细胞系等多种巨噬

图2 α -KG的抗氧化途径Fig 2 Antioxidative channels of α -KG

SOD: superoxide dismutase; CAT: catalase; GSH-Px: glutathione peroxidase; ROS: reactive oxygen species.

细胞模型中,研究者证明 α -KG抑制巨噬细胞的M1促炎表型激活,同时促进M2抗炎表型的极化^[10, 50-53],以减轻炎症。在具体的机制中,LIU等^[51]研究发现 α -KG通过增强M1巨噬细胞中的脯氨酰羟化酶(PHD)活性,抑制核因子 κ B抑制物激酶 β (IKK β)和NF- κ B信号通路激活,从而抑制M1激活。CHENG等^[54]发现 α -KG通过增加过氧化物酶体增殖物激活受体(PPAR γ)的核转运来促进巨噬细胞向M2方向极化。另外, α -KG还通过介导细胞代谢重编程参与巨噬细胞表型极化的调控。 α -KG通过10-11易位家族蛋白(TET)表观途径抑制糖酵解相关基因表达,恢复线粒体耗氧量来逆转促炎巨噬细胞的代谢表型^[10],并通过Jmjd3表观遗传途径降低H3K27me3组蛋白甲基化,增强M2的脂肪酸氧化,促进巨噬细胞向M2极化^[55](图3)。

T细胞浸润在代谢炎症的发生发展中也起到了不可忽视的作用^[49, 56]。近年来研究表明 α -KG在决定T细胞的激活与分化过程中扮演重要角色。CHEN等^[57]在小鼠原代CD4⁺T细胞中发现促炎性T细胞谱系(Th1和Th17)的琥珀酸/ α -KG比率高于幼稚T细胞谱系(Th0)和抗炎谱系(iT_{reg}),添加 α -KG可以通过H3K4me3组蛋白甲基化表观调控转录因子Blimp-1表达,从而抑制促炎性Th1和Th17细胞分化。细胞中高水平的氨会抑制T细胞生长和功能,导致T细胞耗竭^[58]。在此基础上,WEISSHAAR等^[59]发现在体外 α -KG可以增强CD8⁺T细胞中游离氨转化为谷氨酸的能力,实现对氨的解毒作用,恢复T细胞抗慢性炎症反应。

4 α -KG在防治代谢综合征中的应用前景

4.1 α -KG调节体质量和血脂

肥胖往往是代谢综合征中其他成分发生的始动因素,其导致的脂肪代谢异常、胰岛素抵抗和代谢炎症贯穿于代谢综合征发生发展的全过程^[60-61]。 α -KG参与调节脂质稳态(图4)。RADZKI等^[62]利用饮食诱导的高胆固醇血症大鼠模型来确定 α -KG对血脂的影响。接受 α -KG饲喂的实验组大鼠的血清总胆固醇、低密度脂蛋白(LDL)和甘油三酯浓度相较于对照组均下降,高密度脂蛋白(HDL)浓度呈上升趋势,且 α -KG治疗组的体质量显著下降。

脂肪组织中最常见的WAT是导致肥胖的罪魁祸首。相比于WAT,棕色脂肪组织(BAT)和米色脂肪组织则恰恰相反,被激活可通过产热改善肥胖和代谢功能障碍^[63]。YUAN等^[22]发现饮水添加 α -KG显著降低DIO小鼠的腹股沟白色脂肪量,促进白色脂肪分解和棕色脂肪的产热,这可能是 α -KG通过2-氧化戊二酸受体(OXGR1)刺激肾上腺释放肾上腺素实现的。

PRDM16是调节棕色脂肪生成和白色脂肪细胞褐变的关键转录因子^[64]。 α -KG作为TET酶的辅助因子,参与Prdm16表达所必需的DNA去甲基化过程^[35]。TIAN等^[35]发现高脂饲喂的小鼠饮水添加 α -KG后,腹股沟WAT的质量明显减轻,伴随着腹股沟脂肪组织中棕色脂肪相关基因和蛋白质表达的增加。此外, α -KG给药降低白色脂肪量并促进其褐变,可能是通过上调Prdm16启动子中DNA去甲基化激活Prdm16表达^[35]。

此外,CHEN等^[65]提出饮水添加 α -KG可能通过影响肠道微生物群来降低小鼠体质量。多项动物实验^[66-67]提示 α -KG可以用于预防高脂肪饮食以及高果糖饮食小鼠的肥胖。

4.2 α -KG调节血糖

研究者们很早就发现 α -KG可以增强小鼠离体胰岛的胰岛素分泌^[68]。在随后的研究中提出 α -KG可能通过提升ATP/ADP比率,抑制ATP敏感的K⁺(K_{ATP})通道,导致质膜去极化,从而激活胰岛素胞吐^[69-71]。ODEGAARD等^[72]提出 α -KG载体(OGC)介导 α -KG从线粒体转运至胞质以影响胰岛素分泌。通过siRNA抑制大鼠胰岛组织中OGC表达,显著降低葡萄糖刺激后的胰岛素分泌,表明 α -KG需要转运至胞质,刺激胰岛素分泌^[73]。此外,脯氨酰羟化酶(PHD)各亚型在胰岛中均高度表达,对于胰岛素分泌是必需的^[74]。 α -KG作为PHD的辅助因子, α -KG可能通过调节PHD使胰岛素释放相关的关键蛋白质脯氨酸羟化,调节胰岛素分泌^[75-77],提示着 α -KG在血糖调节中的作用。

肝脏和胰腺共同参与血糖的调节,肝脏是摄入食物后处理葡萄糖的主要器官之一,通过糖原合成分解、糖异生等多种代谢途径控制血糖^[78]。 α -KG可通过改善肝脏糖异生作用实现维持血糖稳态的效果^[21]。在饮食诱导的2型糖尿病小鼠模型、db/db小鼠、离体肝脏组织、肝原代细胞等多种模型中,YUAN等^[21]证明 α -KG可以直接作用于肝脏,通过Jmjd3-H3K27me3-serpina1e途径抑制肝脏糖异生作用,介导降血糖作用。

最新研究发现,添加 α -KG可以显著降低在2型糖尿病小鼠的血小板和白细胞(中性粒细胞和单核细胞)活性。 α -KG还可有效抑制pAkt和pP65信号通路,降低白细胞的浸润以及炎症细胞因子的积累,提示 α -KG对高血糖的潜在治疗效果^[79]。

4.3 α -KG改善心血管功能

大量的流行病学研究显示,肥胖、糖尿病和血脂异常是高血压的危险因素,继而增加心血管疾病风险^[80-82]。目前针对代谢综合征相关的高血压首先建议生活方式的改变,但并未向该类高血压患者的药物治疗提供具体建

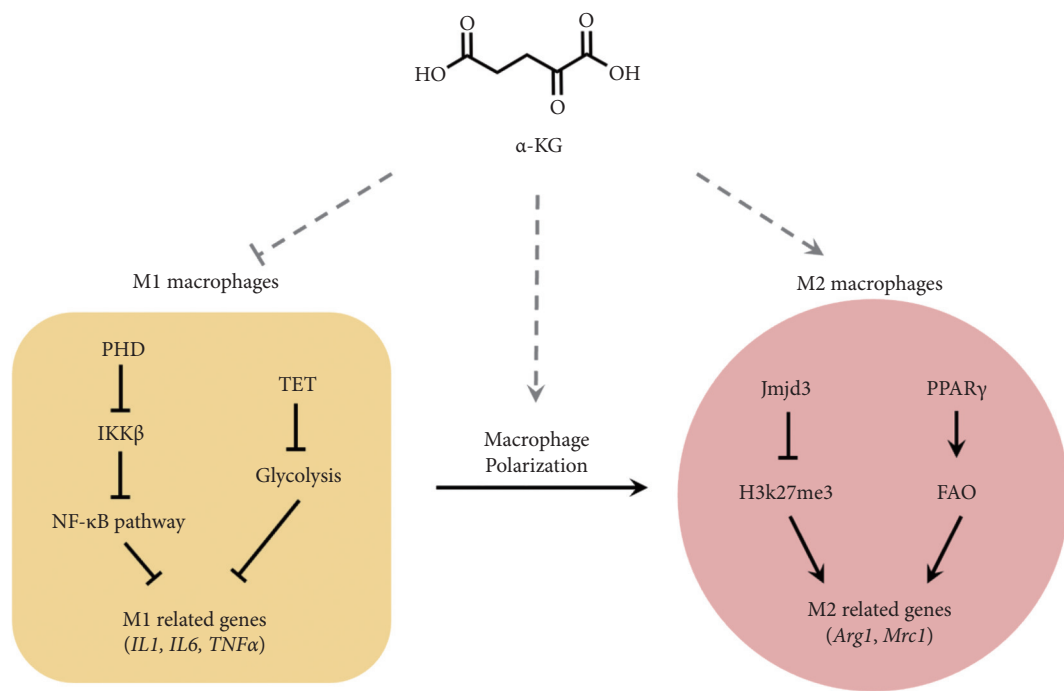


图 3 α -KG调控巨噬细胞的机制通路

Fig 3 The mechanism pathway of α -KG regulating macrophages

PHD: prolyl hydroxylase; IKK β : inhibitory kappa B kinase beta; NF- κ B: nuclear factor kappa B; TET: ten-eleven translocation; *IL1*: interleukin-1; *IL6*: interleukin-6; *TNF α* : tumor necrosis factor alpha; Jmjd3: jumonji domain containing-3; PPAR γ : peroxisome proliferator activated receptor gamma; FAO: fatty acid oxidation; *Arg1*: arginase-1; *Mrc1*: mannose receptor type c-1.

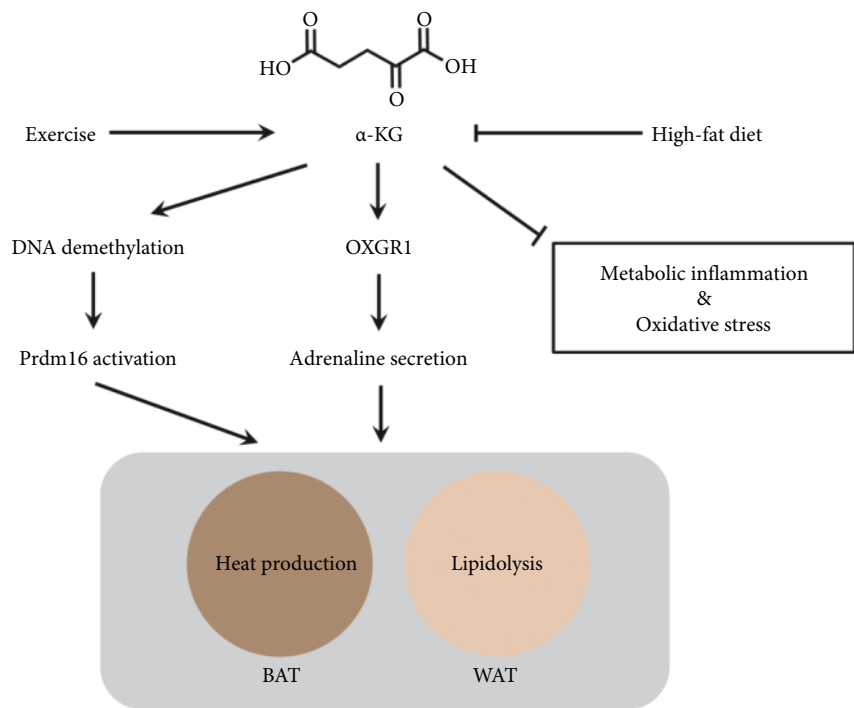


图 4 α -KG改善肥胖的可能机制

Fig 4 Potential mechanism of α -KG improving obesity

DNA: deoxyribonucleic acid; OXGR1: oxoglutarate receptor 1; Prdm16: positive regulatory domain 16; BAT: brown adipose tissue; WAT: white adipose tissue.

议。基于利尿剂和 β 受体阻滞剂的传统抗高血压治疗可能加重其代谢异常^[83]。

直接研究 α -KG是否调节血压的文献较少, OGISO等^[84]发现给血压正常的大鼠静脉或腹腔注射10 mg/kg高剂量

α -KG具有一定的降血压效果。在体外大鼠血管平滑肌细胞中发现 α -KG通过促进胞内钙离子的释放提高舒张相关基因*Mlck*表达,扩大细胞伸展面积^[85],提示 α -KG可能参与血压的调节。

许多实验证据支持改善内皮功能障碍可降低代谢综合征进一步发展成心血管疾病的可能^[86-87]。CHENG等^[46]构建的泊洛沙姆407(P-407)诱导的高脂血症小鼠模型中胸主动脉内膜完整被破坏,内皮组织结构紊乱,提前灌胃给予 α -KG水溶液[50 mg/(kg·d)]9 d可预防性改善胸主动脉的内皮损伤。

在心血管系统中,一氧化氮(NO)生物利用度的缺乏被认为是内皮功能障碍的标志。研究表明口服 α -KG可以改善DIO大鼠的体内血NO含量以及DIO大鼠原代内皮细胞在体外的NO生成^[34, 88]。其中 α -KG参与NO生成的机制包括:①刺激BCAA的转氨分解生成NO^[88];②进入谷氨酰胺代谢,刺激NO前体精氨酸的合成^[89];③通过抑制果糖6-磷酸转氨酶(GFAT)活性,拮抗高脂环境下过多的BCAA对NO生成的抑制作用^[90]。

高血压是造成心脏压力超负荷的首要流行病学原因,首先导致心肌肥大,随着肥大心肌转变为衰竭心肌而出现慢性心力衰竭等心血管疾病^[91]。 α -KG可改善心脏压力超负荷导致的心肌肥大以及心功能不全。AN等^[44]提出饮水补充 α -KG将横主动脉缩窄(TAC)诱导的心衰小鼠的心肌细胞平均横截面积明显降低49.11%,心脏组织中心肌肥大相关基因的转录、翻译水平均明显下降。通过多普勒超声心动图评估TAC小鼠的心脏功能, α -KG明显改善舒张末期左心室前壁和后壁厚度、射血分数等心功能指标^[44, 92]。

5 小结与展望

近年来随着代谢组学等技术的发展,逐渐对机体的细胞代谢进行深入解析。研究发现代谢综合征诸多部分的发生发展与机体 α -KG水平下降有关,通过改变体内 α -KG含量可以调节肥胖程度和血糖、血脂、血压水平。人类循环 α -KG水平同样也会随着年龄的增长逐渐降低,在40~80岁之间大幅下降^[93]。人类饮食中不存在 α -KG,膳食补充 α -KG可以弥补体内 α -KG的不足,因此直接补充是摄取 α -KG的唯一可行途径^[94]。

本文综述了 α -KG与代谢综合征中肥胖、高血脂、高血糖、高血压及其潜在机制的研究进展,从“治标”和“治本”两个角度提示 α -KG是防治代谢综合征的有希望的候选药物成分或膳食补充剂。但是 α -KG在代谢综合征中的调控作用和分子机制仍需要进一步地全面挖掘。

BAYLIAK等^[95]在年轻和中年的果蝇成虫中发现了 α -KG的相反疗效。 α -KG降低年轻果蝇的甘油三酯水平,但是中年果蝇的甘油三酯水平却被 α -KG提高。因此,未来的研究需要在更多的哺乳动物模型中讨论 α -KG在代谢综合征中的应用价值。

最后,肥胖、高血压、高血糖、高血脂这四者在代谢综合征中具有相同的病理机制。虽然人体中这四者往往多病并存,但是现阶段临床药物治疗仍然倾向于各方面单独针对性控制。目前 α -KG的相关研究也同样地处于针对血糖、血脂、肥胖等单方面论证的阶段。相关研究表明, α -KG可改善胰岛素抵抗、氧化应激和慢性炎症。那么 α -KG能否通过参与代谢综合征共同的病理机制,从而整体性地改善机体代谢紊乱,实现当前倡导的“异病同治”的目标^[96],这也是需要在更综合性的代谢综合征疾病模型中进一步探究的要点之一。

* * *

作者贡献声明 李雨含负责论文构思、可视化和初稿写作,王璆负责论文构思、经费支持和审读与编辑写作,袁泉负责研究项目管理、提供资源、监督指导、经费支持和审读与编辑写作。所有作者已经同意将文章提交给本刊,且对将要发表版本进行最终定稿,并同意对工作的所有方面负责。

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